Serum estradiol above the postmenopausal level after chemotherapy-induced amenorrhea in breast cancer patients

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Background: Cytotoxic drugs suppress ovarian function and induce permanent or transient amenorrhea in one- to two-thirds of women. Suppression of ovarian function is effective therapy for premenopausal women with hormone receptor-positive breast cancer. Aromatase inhibition is effective for postmenopausal women with hormone receptor-positive breast cancer, but is not indicated in premenopausal women. **Objective:** We aim to determine whether, and for how long, ovarian estrogen production persists after chemotherapy-induced amenorrhea. **Materials & methods:** Serum estradiol, follicle-stimulating hormone and luteinizing hormone levels were determined in 56 breast cancer patients, 1–34 months after the onset of chemotherapy-induced amenorrhea. In 18 patients, these values were determined more than once. Postmenopausal estradiol levels are less than 10 pg/ml, follicle-stimulating hormone and luteinizing hormone greater than 20 mIU/ml. **Results:** The estradiol level was greater than 9 pg/ml at least once in 42 out of 56 patients. For 75 determinations, the estradiol level ranged from less than 10 to 344 pg/ml, with a median of 25 pg/ml and a mean of 41 pg/ml. Estradiol levels were not significantly correlated with either the number of months after the onset of amenorrhea at which they were drawn, or follicle-stimulating and luteinizing hormone levels. **Conclusions:** Ovarian estradiol production often persists for 1 year or more after chemotherapy-induced amenorrhea.

Estrogen stimulates the growth of hormone receptor-positive (HR+) breast cancer (BC). Even postmenopausal estrogen concentrations can maintain proliferation of HR+ breast tumor cells *in vitro* [1,2].

Adjuvant chemotherapy significantly increases relapse-free survival of premenopausal women with node-positive and larger node-negative BC [3]. Chemotherapy induces menopause in up to 50% of women aged under 40 years, and in up to 86% of women aged over 40 years [4,5], which may improve the outcome in HR+ patients [6,7]. Ovarian suppression by luteinizing hormone-releasing hormone (LH-RH) agonists and tamoxifen without chemotherapy is effective adjuvant treatment of BC in HR+ patients [8,9]. Therefore, menopause induction by chemotherapy is likely to contribute to its efficacy in the adjuvant treatment of HR+ BC patients. In postmenopausal women with HR+ tumors, aromatase inhibitors (AIs) are as (or more) effective adjuvant therapy than tamoxifen [10]. These agents are not employed in premenopausal women since they do not suppress, and may enhance, ovarian estrogen production [11]. Their efficacy and safety in perimenopausal amenorrheic women in whom some ovarian estrogen production persists is not known.

Serum estradiol (E2) is known to remain above postmenopausal levels for 6–12 months after menstruation ceases in 20–40% of women undergoing natural menopause [12]. The development of amenorrhea during or after chemotherapy cannot, therefore, be considered conclusive evidence that ovarian function has entirely ceased. The status of ovarian function cannot be determined from menstrual history in younger women who have previously had hysterectomies, but are not known to have had bilateral oophorectomies. In these groups of patients, serum E2, follicle-stimulating hormone (FSH) and LH levels may help to decide whether or not LH-RH agonists or AIs are indicated for those with HR+ tumors. Therefore, we determined serum levels of these hormones in 56 women who ceased to menstruate after chemotherapy, and in nine women who had undergone hysterectomy prior to presentation with BC.

Materials & methods

Premenopausal women presenting with BC between 1999 and 2005 were prospectively studied. The only patients included were those whose first systemic treatment was chemotherapy.

Keywords: breast cancer, chemotherapy, estrogen, menopause, ovarian function

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Serum hormone levels were only determined in women who had never been treated with tamoxifen, LH-RH or an AI. All patients had missed at least one menstrual period after the initiation of chemotherapy. In addition, patients who had undergone hysterectomy prior to presentation with BC were studied.

Serum E2 (E2–6-III), FSH and LH levels were determined by immunoassays more than 1 month after the first missed menstrual period and were repeated at various intervals in some patients. Standard premenopausal levels of E2, FSH and LH by these techniques are greater than 100 pg/ml, less than 20 mIU/ml and less than 20 mIU/ml, respectively. E2 levels of less than 100 but greater than 10 pg/ml imply persistent ovarian function, even in patients who have ceased to menstruate. Chemotherapeutic regimens included cyclophosphamide with either doxorubicin (CA), doxorubicin and 5-fluorouracil (CAF), methotrexate and 5-fluorouracil (CMF), or paclitaxel (PTX).

Results

Serum E2, FSH and LH levels were determined at least once in 56 women who ceased to menstruate after the initiation of chemotherapy for BC, and at least twice in 18 out of 56, for a total of 76 determinations. Patient attributes and results are summarized in **Table 1**. The E2 levels of 56 out of 76 determinations were at least 10 pg/ml, and 42 out of 56 patients had at least one E2 level of at least 10 pg/ml. E2 levels 10 pg/ml or greater (range: 10–344 pg/ml; median: 32 pg/ml) were found in 32 determinations from 28 patients obtained at least 6 months (6–31 months; median: 9 pg/ml) after the onset of amenorrhea. Menstruation ultimately resumed in five out of 56 patients, although estradiol levels reached greater than 100 pg/ml in only two out of five patients, even when determined as long as 15 months after the onset of amenorrhea. There was no significant correlation between E2 levels and the intervals after the onset of amenorrhea at which they were determined (crude Pearson correlation between E2 and interval = -0.09, p = 0.457).

The FSH and LH levels in 16 out of 20 patients with E2 levels less than 10 pg/ml were in the postmenopausal range. FSH and LH levels were also high in most patients with E2 levels of 10–64 pg/ml. In the nine patients with E2 levels greater than 64 pg/ml, FSH and LH levels were relatively low (**Table 2**). However, overall there was only minimal correlation between E2 levels and FSH or LH levels (crude Pearson correlations between E2 and FSH = -0.26, p = 0.026; between E2 and LH = -0.22; p = 0.077). As expected, there was a trend towards a higher age in patients with E2 less than 10 pg/ml (median: 48 pg/ml, mean: 46 pg/ml) than in those whose E2 level was greater than 10 pg/ml on at least one determination (median and mean: 43 pg/ml).

Table 1. Summary of serum estradiol, FSH and LH levels of 56 breast cancer patients determined after chemotherapy-induced amenorrhea.

	n	Range	Median	Mean
Patients	56			
Hormone levels*	75			
Age (years)		32–56	45	45
Interval‡		1–34	9	6
E2§		<10–344	25	41
E2 < 10 pg/ml	20			
E2 ≥ 10 pg/ml	55	10–344	41	38
Number of patients with E2 > 10 pg/ml	42			
FSH¶		0–127	47	44
LH#		0–90	36	33

**Total number of E2, FSH and LH levels determined, including successive determinations in the same patient.*

‡Number of months after first missed menstrual period when serum hormone levels were determined.

§Serum estradiol level (pg).

¶Serum FSH level (pg).

#Serum LH level (pg).

E2: Estradiol; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

Table 2. Correlations between estradiol and FSH/LH levels, and months elapsed after onset of amenorrhea.

	n	FSH (pg/ml)			LH (pg/ml)			Interval (pg/ml)		
		Range	*Median*	*Mean*	*Range*	*Median*	*Mean*	*Range*	*Median*	*Mean*
E2 < 10 pg/ml	20	6–122	58	55	4–85	34	36	2–34	5	8
E2 10–64 pg/ml	44	2–127	44	48	0–90	31	34	1–31	7	16
E2 > 64 pg/ml (73–344)	9	0–56	15	19	3–37	17	19	1–12	4	5

E2: Estradiol; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

The chemotherapy regimens employed initially in these patients, and the E2 levels following amenorrhea associated with each regimen, are summarized in Table 3. Patients treated with PTX tended to have higher E2 levels than those treated with CA, CAF or CMF; a smaller percentage of the PTX-treated patients had E2 levels of 10 pg/ml or less, although these differences were not significant (p = 0.257).

E2 levels were determined in nine patients in whom hysterectomies had been performed prior to the onset of BC, before initiation of chemotherapy. E2 was less than 10 pg in three patients, and 11–111 pg (mean: 49 pg, median: 28 pg) in six out of nine. The E2 level was greater than 100 pg in two out of nine patients.

Discussion

We found that E2 levels of women who ceased to menstruate after chemotherapy, as in those in whom amenorrhea occurs naturally [12], often remain above the postmenopausal range for many months. There was a trend to higher post-amenorrhea E2 levels and fewer patients with levels of 10 pg/ml or less in women treated with PTX, rather than CA or CMF, although the differences were not significant. The fact that the addition of taxanes to other chemotherapeutic regimens does not increase the incidence of menopause [13,14] also suggests that these agents have a relatively small effect on ovarian function. Although most of our patients' E2 levels were lower (<100 pg/ml) than those of menstruating women, there is *in vitro* evidence that even post-menopausal E2 levels can sustain BC cell proliferation [1,2]. This is confirmed *in vivo* by the efficacy of endocrine therapy in late postmenopausal women, almost all of whose E2 levels are less than 10 pg/ml. FSH was at post-menopausal levels in many patients with E2 levels of at least 10 pg/ml, perhaps because their few remaining follicles produced more E2 than inhibin, the major inhibitor of pituitary FSH production [15,16].

Two out of nine patients who had undergone hysterectomy appeared to be premenopausal, with E2 levels greater than 100 pg/ml and correspondingly low FSH and LH levels. In the absence of a surgical pathology report confirming bilateral oophorectomy at the time of hysterectomies performed in patients prior to their presentation with BC, there is a case for routine serum hormone determinations in HR+ patients for whom endocrine therapy is contemplated.

Adequately powered controlled studies are needed to determine whether or not ovarian suppression is indicated in amenorrheic women with HR+ tumors whose E2 levels are at least 10 pg.

Aromatase inhibitors are useful in postmenopausal women, but are not indicated in premenopausal women since they cannot suppress, and may increase, ovarian estrogen production; their use may be associated with resumption of ovarian function after chemotherapy-induced amenorrhea [17]. Their effect on ovarian function in amenorrheic perimenopausal women whose E2 levels remain at 10 pg/ml or greater should be determined. There is a case for defining menopause biochemically in perimenopausal women, rather than relying on menstrual history alone.

Table 3. Chemotherapeutic Regimens that induced amenorrhea and estradiol levels after menstruation ceased.*

Regimen	Patients (n)	Median E2	E2 ≤ 10 pg/ml n (%)
All	56	24	16 (26)
CMF	16	19	7 (44)
CA/CAF	27	20	7 (26)
PTX	13	39	2 (15)

**In patients whose post-amenorrhea E2 level was determined more than once, the level found after the longest interval is recorded.*
CA: Cyclophosphamide plus doxorubicin; CAF: Cyclophosphamide, doxorubicin and 5-fluorouracil; CMF: Cyclophosphamide, methotrexate and 5-fluorouracil; PTX: Paclitaxel.

Disclaimer

Part of this data has been published in [18].

Highlights

- We determined serum estradiol, follicle-stimulating and luteinising hormone levels in 56 breast cancer patients who had ceased to menstruate after the initiation of cytotoxic chemotherapy. Almost all proved to have become permanently menopausal.
- Nevertheless, in 42 of these 56 women, serum estadiol remained above the postmenopausal level for a median of 6 months after the last menstrual period, while follicle-stimulating and luteinising hormones were often below the postmenopausal level.
- Such data may be relevant to decisions concerning aromatase inhibitor therapy, as these agents are contraindicated in premenopausal patients.

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